

CLINICAL CARDIOLOGY

Optimal Diets for Prevention of Coronary Heart Disease

Frank B. Hu, MD, PhD

Walter C. Willett, MD, DrPH

THE RELATIONSHIP BETWEEN DIET and coronary heart disease (CHD) has been studied intensively for nearly a century. In 1908, Ignatowski produced atherosclerosis in rabbits with a diet high in cholesterol and saturated fat¹; feeding the rabbits cholesterol alone produced identical lesions. In the early 1950s, controlled feeding studies demonstrated that saturated fatty acids and, to a lesser extent, cholesterol increased serum cholesterol concentration in humans.² Meanwhile, epidemiologic studies found that increased serum cholesterol predicted risk of CHD in human populations. These discoveries led to the classic diet-heart hypothesis, which postulated a primary role of dietary saturated fat and cholesterol in the cause of atherosclerosis and CHD in humans.³ The diet-heart hypothesis gained further support from ecological correlations relating saturated fat intake to rates of CHD in cohorts from different countries⁴ and from studies of migrants from low- to high-risk countries.⁵

Until recently, most epidemiologic and clinical investigations of diet and CHD have been dominated by the diet-heart hypothesis. However, the original hypothesis was overly simplistic because the effects of diet on CHD can be mediated through multiple biological pathways other than serum total cholesterol or low-density lipoprotein cholesterol (LDL-C) (FIGURE 1).⁶ The existence of these multiple pathways heightens the need to study clinical outcomes because the use of a single in-

Context Coronary heart disease (CHD) remains the leading cause of mortality in industrialized countries and is rapidly becoming a primary cause of death worldwide. Thus, identification of the dietary changes that most effectively prevent CHD is critical.

Objective To review metabolic, epidemiologic, and clinical trial evidence regarding diet and CHD prevention.

Data Sources and Study Selection We searched MEDLINE through May 2002 for epidemiologic and clinical investigations of major dietary factors (fat, cholesterol, omega-3 fatty acids, *trans*-fatty acids, carbohydrates, glycemic index, fiber, folate, specific foods, and dietary patterns) and CHD. We selected 147 original investigations and reviews of metabolic studies, epidemiologic studies, and dietary intervention trials of diet and CHD.

Data Extraction Data were examined for relevance and quality and extracted by 1 of the authors.

Data Synthesis Compelling evidence from metabolic studies, prospective cohort studies, and clinical trials in the past several decades indicates that at least 3 dietary strategies are effective in preventing CHD: substitute nonhydrogenated unsaturated fats for saturated and *trans*-fats; increase consumption of omega-3 fatty acids from fish, fish oil supplements, or plant sources; and consume a diet high in fruits, vegetables, nuts, and whole grains and low in refined grain products. However, simply lowering the percentage of energy from total fat in the diet is unlikely to improve lipid profile or reduce CHD incidence. Many issues remain unsettled, including the optimal amounts of monounsaturated and polyunsaturated fats, the optimal balance between omega-3 and omega-6 polyunsaturated fats, the amount and sources of protein, and the effects of individual phytochemicals, antioxidant vitamins, and minerals.

Conclusions Substantial evidence indicates that diets using nonhydrogenated unsaturated fats as the predominant form of dietary fat, whole grains as the main form of carbohydrates, an abundance of fruits and vegetables, and adequate omega-3 fatty acids can offer significant protection against CHD. Such diets, together with regular physical activity, avoidance of smoking, and maintenance of a healthy body weight, may prevent the majority of cardiovascular disease in Western populations.

JAMA. 2002;288:2569-2578

www.jama.com

termediate end point as a surrogate of CHD risk could be misleading. In the past 2 decades, understanding of the nutrients and foods likely to promote cardiac health has grown substantially owing to studies of the molecular mechanisms of atherosclerosis and the metabolic effects of various nutrients and foods, large and carefully conducted prospective cohort investigations, and dietary intervention trials. Although the search for the optimal diet

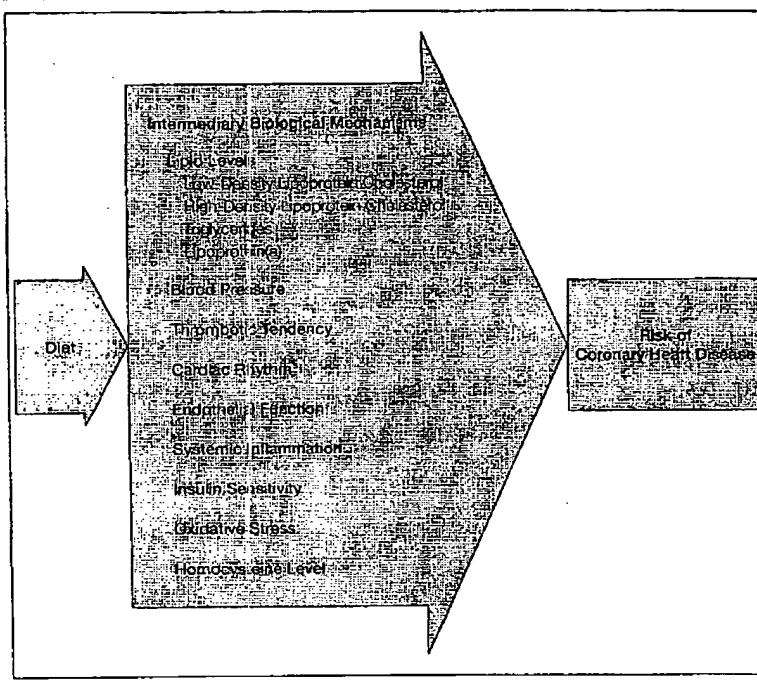
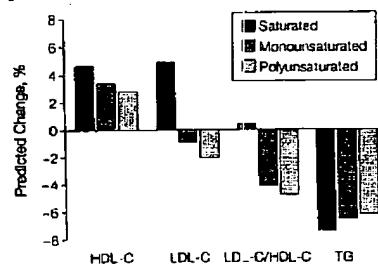
for prevention of CHD is far from over, more specific and firmer evidence on diet and CHD is now available.

Author Affiliations: Departments of Nutrition and Epidemiology, Harvard School of Public Health, and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass.

Corresponding Author and Reprints: Frank B. Hu, MD, PhD, Department of Nutrition, Harvard School of Public Health, 655 Huntington Ave, Boston, MA 02115 (e-mail: frank.hu@channing.harvard.edu).

Clinical Cardiology Section Editor: Michael S. Lauer, MD, Contributing Editor.

OPTIMAL DIETS FOR PREVENTION OF CHD

Figure 1. Mechanisms by Which Diet Potentially Influences Risk of Coronary Heart Disease**Figure 2. Predicted Changes in Serum Lipids and Lipoproteins**

Predicted changes are based on replacement of 5% of energy as carbohydrates with specific fatty acids under isocaloric conditions, assuming baseline high-density lipoprotein cholesterol (HDL-C) levels of 50 mg/dL (1.30 mmol/L), low-density lipoprotein cholesterol (LDL-C) levels of 130 mg/dL (3.37 mmol/L), and triglyceride (TG) levels of 150 mg/dL (1.70 mmol/L).¹⁰

METHODS

For this review, we searched MEDLINE through May 2002 for epidemiologic and clinical investigations of various di-

etary factors (fat, cholesterol, omega-3 fatty acids, trans-fatty acids, carbohydrates, glycemic index, fiber, folate, specific foods, and dietary patterns) and CHD. We selected 147 original investigations and reviews of metabolic studies, epidemiologic studies, and dietary intervention trials relating to diet and CHD. Data were examined for relevance and quality and extracted by 1 of the authors. Although we emphasized controlled trials with clinical end points, few such trials exist. Thus, we gave substantial weight to large prospective cohort studies that reported disease outcomes and metabolic studies with established intermediate end points. The evidence is considered strongest when results from different types of studies are consistent.

DIETARY FAT**Metabolic Effects of Dietary Fatty Acids**

Numerous controlled feeding studies of the effects of different dietary fatty acids

on serum cholesterol levels have been summarized in several meta-analyses from which predictive equations have been developed.⁷⁻¹¹ All such analyses confirm early reports by Keys⁷ and Hegsted⁸ that saturated fatty acids increase and polyunsaturated fatty acids decrease total and LDL cholesterol. All 3 classes of fatty acids (saturated, monounsaturated, and polyunsaturated) elevate high-density lipoprotein cholesterol (HDL-C) when they replace carbohydrates in the diet, and this effect is slightly greater with saturated fatty acids (FIGURE 2). Also, triglyceride levels increase when dietary fatty acids are replaced by carbohydrates. Because replacement of saturated fat with carbohydrates proportionally reduces both LDL-C and HDL-C, and, thus, has little effect on the LDL-HDL ratio and increases triglycerides, this change in diet would be expected to have minimal benefit on CHD risk. However, when monounsaturated or polyunsaturated fats replace saturated fat, LDL-C decreases and HDL-C changes only slightly. Moreover, substituting polyunsaturated fat for saturated fat may have beneficial effects on insulin sensitivity^{12,13} and type 2 diabetes.^{14,15}

In numerous controlled metabolic studies, trans-fatty acids (found in stick margarine, vegetable shortenings, and commercial bakery and deep-fried foods) have been shown to raise LDL-C levels and lower HDL-C relative to cis-unsaturated fatty acids,¹⁶⁻²⁴ and the increase in the ratio of total to HDL cholesterol for trans-fat is approximately twice that for saturated fat (FIGURE 3).²⁵ Trans-fat increases plasma levels of lipoprotein a^{18,23} and triglycerides²⁶ and may reduce endothelial function by impairing flow-mediated dilation.²⁷ In addition, trans-fatty acids adversely affect essential fatty acid metabolism and prostaglandin balance by inhibiting the enzyme delta-6 desaturase.^{28,29} Finally, high intake of trans-fat may promote insulin resistance³⁰ and increase risk of type 2 diabetes.¹³

Epidemiologic Studies

Geographic and migration studies showed strong positive correlations be-

OPTIMAL DIETS FOR PREVENTION OF CHD

tween saturated fat intake and rates of CHD.^{43,51} Although these data provide evidence for the importance of environmental factors in the cause of CHD, they are seriously confounded by other aspects of diet, other lifestyle factors, and economic development. Prospective cohort studies of individuals can better control for potential confounding factors. Despite long-standing interest in the diet-heart hypothesis, prospective studies of diet and CHD are surprisingly few³²⁻⁴⁰; only 2 found a significant positive association between saturated fat intake and risk of CHD.^{35,36} However, most earlier studies were limited by small study size, inadequate dietary assessment, or incomplete adjustment for confounding.⁴¹

The largest and most detailed analysis included 4 repeated measures of diet over 14 years among 80 082 women in the Nurses' Health Study cohort.⁴⁰ Higher intakes of trans-fat and, to a smaller extent, saturated fat were associated with increased risk, whereas higher intakes of nonhydrogenated polyunsaturated and monounsaturated fats were associated with decreased risk. Because of opposing effects of different types of fat, total fat as percentage of energy was not appreciably associated with CHD risk. Dietary cholesterol and modest egg consumption (1 egg per day) were not significantly associated with either CHD or stroke.⁴²

In addition to the Nurses' Health Study, 3 other large prospective studies have consistently found elevated risk of CHD with higher trans-fat intake.^{38,39,43} Combining the results of the 4 prospective studies, the pooled relative risk of CHD associated with a difference of 2% energy in trans-fatty acid intake (assessed at baseline) was 1.25 (95% confidence interval, 1.11-1.40).⁴³ Results from case-control studies using biochemical markers of trans-fat intake have been less consistent.²⁵ In a recent population-based case-control study of 179 cardiac arrest patients and 285 community controls, higher red-cell membrane levels of trans-fatty acids, especially trans-isomers from partially hydrogenated

vegetable oils, were associated with significantly increased risk of primary cardiac arrest.⁴⁴ No association was seen in a small UK study of sudden death.⁴⁵

Trials of Change in Dietary Fat

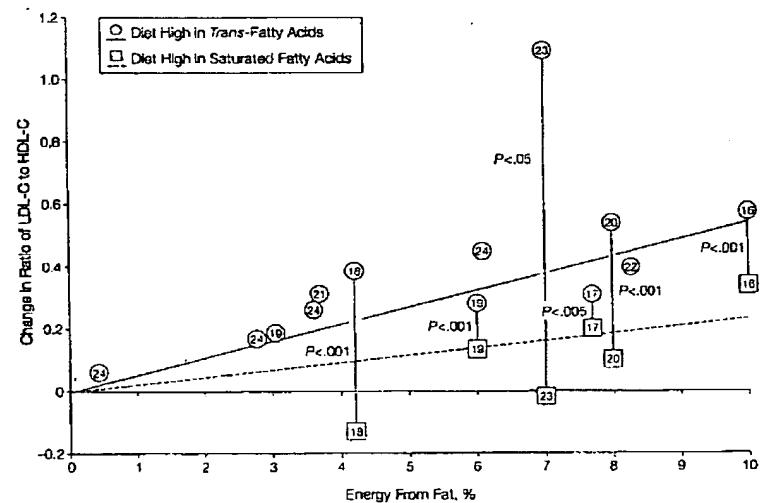
Only a handful of dietary trials with CHD end points have been conducted and most were among patients with CHD (TABLE). Two dietary approaches were tested in earlier trials; one replaced saturated fat with polyunsaturated fat, leaving total fat unchanged; the other lowered total fat. In all the high-polyunsaturated-fat trials,⁴⁶⁻⁵¹ serum cholesterol was significantly reduced. In the Finnish Mental Hospital Study,⁴⁷ soft margarine replaced stick margarine, so the reduction in CHD was probably in part due to reduction in trans-fat intake. In the Minnesota Coronary Survey,⁵¹ cardiovascular events were not significantly reduced by a high-polyunsaturated-fat diet despite a decrease in serum cholesterol, but the mean duration of dietary intervention was only about 1 year. Two secondary

prevention trials testing the approach of total fat reduction did not find a significant reduction in serum cholesterol or CHD events.^{52,53}

Omega-3 Fatty Acids

Omega-3 fatty acids may reduce risk of CHD by preventing cardiac arrhythmia, lowering serum triglyceride levels, decreasing thrombotic tendency, and improving endothelial dysfunction.^{54,55} An inverse association between fish intake and coronary mortality was first reported in a Dutch population,⁵⁶ and more than 15 prospective studies have followed. A systematic review of the 11 studies published before 2000 concluded that the inverse association was stronger for fatal CHD than for nonfatal myocardial infarction (MI), and the benefit was most evident in populations with higher-than-average risk of CHD.⁵⁷ Since that review, 4 additional prospective cohort studies⁵⁸⁻⁶¹ and 1 case-control study⁶² have provided further support for the protective effects of marine omega-3 fatty

Figure 3. Results of Metabolic Studies of the Effects of a Diet High in Trans or Saturated Fatty Acids on the Ratio of LDL-C to HDL-C



LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. A diet with isocaloric amounts of cis-fatty acids was used as the comparison group. References are indicated by numbers inside data markers. The solid line indicates the best-fit regression for trans-fatty acids. The dashed line indicates the best-fit regression for saturated fatty acids. Reprinted with permission.²³

OPTIMAL DIETS FOR PREVENTION OF CHD

acids against CHD in diverse populations. Notably, 2 recent studies have shown that consuming 2 or more servings of fish per week was associated with 30% lower risk of CHD in women⁶⁰ and that blood levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were strongly associated with decreased risk of sudden cardiac death in men.⁶¹

α -Linolenic acid (ALA), an omega-3 fatty acid high in flaxseed, canola, and soybean oils, can be converted to EPA

and DHA in humans and, thus, may have a role in prevention of CHD. An inverse association between intake of ALA and risk of fatal CHD was observed in most prospective cohort studies,^{38,39,63,64} but not in 1 smaller study.⁶⁵ In a cohort of women, frequent consumption of oil-and-vinegar salad dressing (a major source of ALA in US diets) was associated with a significantly lower risk of fatal CHD.⁶³

Three clinical trials have examined the effects of omega-3 fatty acids in sec-

ondary prevention of CHD (Table). In the Diet and Reinfarction Trial,⁵³ patients advised to eat fish twice weekly or to take fish oil (1.5 g/d) had a 29% lower mortality after 2 years. In the GISSI-Prevenzione trial,⁶⁶ daily supplementation with EPA plus DHA (1 g/d) reduced the main end point (composite of death, nonfatal MI, and stroke) by 15%, primarily because of a 45% reduction in sudden death after 3 months of treatment.⁶⁷ A trial from India suggested benefits of both fish oil and mus-

Table. Trials of Dietary Interventions and Coronary Events*

Trial	Patients in Intervention Group	Dietary Intervention	Dietary Fat (Energy) In Treatment Group, %	Energy From P and S Fat In Treatment Group, %	Overall Trial Duration, y	Change in Serum Cholesterol Level, %†	Change in CHD, %‡
Low-Fat Approach							
MRC (low fat) ⁵²	123 male MI patients	Reduce total fat	22	NR	3	-5	+4
DART ⁵³	1015 male MI patients	Reduce total fat	32	NR	2	-4	-9
High-Polyunsaturated-Fat Approach							
Finnish Mental Hospital Study ⁴⁷	676 men without CHD	Reduce saturated fat, increase polyunsaturated fat	35	P = 13; S = 9	6	-15	-44§
Los Angeles Veteran Study ⁴⁸	424 men; most had no evidence of existing CHD	Reduce saturated fat, increase polyunsaturated fat	40	P = 16; S = 9	8	-13§	-20 in CHD, -31§ in cardiovascular events
Oslo Diet-Heart Study ^{49,54}	206 male MI patients	Reduce saturated fat, increase polyunsaturated fat	39	P = 21; S = 9	5	-14§	-25§
MRC (soy oil) ⁵⁰	199 male MI patients	Reduce saturated fat, increase polyunsaturated fat	48	P:S ratio = 2	4	-15§	-12
Minnesota Coronary Survey ⁵¹	4393 men and 4664 women	Reduce saturated fat, increase polyunsaturated fat	38	P = 15; S = 9	1	-14§	0
Increase Omega-3 Fatty Acid							
DART ⁵³	1015 male MI patients	Fish twice per week or fish oil (1.5 g/d)	NR	NR	2	NR	-16 in CHD events, -29§ in total mortality
GISSI-Prevenzione ^{56,67}	5666 MI patients, primarily men	Fish oil (EPA + DHA, 1 g/d)	NR	NR	3.5	0	-30§ in cardiovascular death, -45§ in sudden death
Indian Experiment of Infarct Survival ⁴⁸	242 MI patients, primarily men	Fish oil (EPA, 1.08 g/d) or mustard oil (ALA, 2.9 g/d)	NR	NR	1	0	-30§ in fish oil group, -19 in mustard oil group
Whole-Diet Approach							
Lyon Diet Heart Study ^{58,70}	302 MI patients, primarily men	High ALA intake and Mediterranean diet	31	P:S ratio = 0.7	3.8	0	-72§
Indian Experiment of Infarct Survival ¹¹	204 MI patients, primarily men	High intake of fruits, vegetables, nuts, fish, and pulses	24	P:S ratio = 1.2	1	-9§	-40§

*Adapted from Hu et al.¹¹ P indicates polyunsaturated fat; S, saturated fat; CHD, coronary heart disease; MRC, Medical Research Council; MI, myocardial infarction; NR, not reported; DART, Diet and Reinfarction Trial; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; and ALA, α -linolenic acid.

†Change in cholesterol level refers to the percentage change in serum cholesterol level in the treatment group compared with the change in the control group.

‡Change in CHD refers to the percentage difference in coronary event rates in the treatment group compared with the control group.

§P < .05.

||The total duration of the study was 4.5 years, but the mean duration of the intervention was only 1 year.

OPTIMAL DIETS FOR PREVENTION OF CHD

tard oil in the treatment of MI patients.⁶⁸ In the Lyon Diet Heart Study, higher ALA consumption in the context of a Mediterranean diet dramatically reduced total and cardiovascular mortality as well as nonfatal MI.^{69,70} These trials strongly support the protective effects of omega-3 fatty acids, including both ALA and fish oil, in secondary prevention of CHD. The role of fish oil supplements in primary prevention of CHD has not been tested.

CARBOHYDRATES

Prevailing dietary recommendations have emphasized high intake of complex carbohydrates, mainly starch, and avoidance of simple sugars.^{71,72} However, many starchy foods, such as baked potatoes and white bread, are rapidly digested to glucose and produce even higher glycemic and insulinemic responses than sucrose (half glucose and half fructose). The glycemic index (GI) ranks foods based on rise in blood glucose (the incremental area under the curve for blood glucose levels) after ingestion compared with glucose or white bread, standardizing the carbohydrate content to 50 g.^{73,74} Foods with a low degree of starch gelatinization (more compact granules), such as spaghetti and oatmeal, and a high level of viscose soluble fiber, such as barley, oats, and rye, tend to have a slower rate of digestion and, thus, lower GI values. In several controlled clinical studies,⁷⁵ feeding low-GI meals to diabetic patients led to significant improvement in glycemic control and lipid profile, but larger studies are needed.

Glycemic load (GL; the product of the GI value of a food and its carbohydrate content) has been used to represent both the quality and quantity of the carbohydrates consumed.^{76,77} Dietary GL is more strongly associated with higher fasting triglycerides and lower HDL-C levels compared with GI.⁷⁸ A strong positive association between GL and risk of CHD was observed among 75521 women during 10 years of follow-up.⁷⁹ The increased risk was more pronounced among overweight and obese women, consistent with meta-

bolic studies that the adverse effects of a high GL diet are exacerbated by underlying insulin resistance.⁸⁰ Thus, carbohydrate-containing foods should not be judged simply by their GI values; the amount of carbohydrates, fiber, and other nutrients are also important.

Another way to classify dietary carbohydrates is to subdivide cereal grains—staple foods in most societies—into whole and refined grains. Most cereal grains are highly processed before they are consumed. Refined grain products contain more starch but substantially lower amounts of dietary fiber, essential fatty acids, and phytochemicals, although these products are typically enriched with some vitamins and minerals. In several epidemiologic studies, higher consumption of whole grains was associated with lower risk of CHD. Also, prospective cohort studies have consistently found an inverse association between fiber intake and risk of CHD.⁸¹ Several studies have found a stronger association for cereal fiber than for fruit or vegetable fiber.⁸²⁻⁸⁴ The inverse association for fiber observed in epidemiologic studies cannot be fully explained by its cholesterol-lowering effects; the low GI of foods with a high level of fiber and numerous micronutrients in whole grains may also contribute to the benefits.⁸⁵

FOLATE

Much evidence suggests that adequate folate consumption is important for the prevention of CHD. Epidemiologic studies have found an inverse association between folate intake measured by dietary questionnaire or serum folate level and risk of CHD,⁸⁶⁻⁹⁰ which is likely to be mediated through homocysteine-lowering effects of folic acid. Two randomized placebo-controlled trials evaluated effects of folic acid supplementation on the development and progression of atherosclerosis. Vermeulen et al⁹¹ found that supplementation with folic acid and vitamin B₆ for 2 years significantly decreased subclinical atherosclerosis indicated by abnormal exercise electrocardiography tests among siblings of patients with existing car-

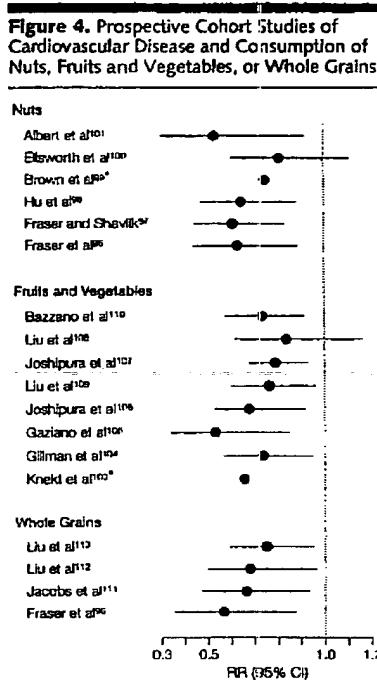
diovascular disease. In the Swiss Heart Study, treatment with a combination of folic acid and vitamins B₆ and B₁₂ significantly decreased restenosis and revascularization after coronary angioplasty at 6 months⁹² and a combined cardiovascular end point at 11 months.⁹³ Ongoing clinical trials should provide more definitive data on the role of folic acid supplementation in CHD prevention, but the interpretation of the findings from trials conducted in the United States could be complicated by the fortification of flour with folic acid.⁹⁴

SPECIFIC FOODS AND DIETARY PATTERNS

The relationship between consumption of specific foods or overall dietary patterns and risk of CHD has been examined in recent studies. Such analyses are valuable in evaluating additional diet-heart hypotheses and in making practical dietary recommendations. For example, replacement of red meat with chicken and fish has been associated with reduced risk of CHD.⁹⁵ An inverse association between nut consumption and risk of CHD has been seen consistently in prospective studies.⁹⁶⁻¹⁰¹ (FIGURE 4), which further underscores the importance of distinguishing different types of fat. Although nuts are high in fat and, thus, routinely proscribed in dietary recommendations, the predominant types of fat in nuts are monounsaturated and polyunsaturated, which lower LDL-C level.¹⁰²

Although beneficial effects of fruits and vegetables are widely assumed, only in recent years has solid epidemiologic evidence begun to emerge¹⁰³⁻¹¹⁰ (Figure 4). In the largest study, including 84251 women and 42148 men,¹⁰⁷ Joshipura et al reported a significant inverse association between consumption of fruits and vegetables, particularly green leafy vegetables and vitamin C-rich fruits and vegetables, and risk of CHD. Increased consumption of potatoes, however, was not associated with benefits. In several prospective studies, a higher consumption of whole grains as opposed to refined grains was

OPTIMAL DIETS FOR PREVENTION OF CHD



Relative risks (RRs) and 95% confidence intervals (CIs) were derived from the comparison of the incidence rates between the highest- and lowest-consumption groups (quintiles, quartiles, or specific intake categories) and were adjusted for nondietary and/or dietary covariates. In each category, studies are shown in the order of most recent to least recent publication. Asterisk indicates confidence intervals were not published in the original article.

associated with a lower risk of cardiovascular disease (Figure 4).^{96,111-113}

Recently, several studies have reported the role of overall dietary patterns in predicting long-term risk of CHD.¹¹⁴ In these analyses, a "prudent" pattern characterized by higher intakes of fruits, vegetables, legumes, whole grains, poultry, and fish was associated with lower risk of CHD, whereas a "Western" pattern characterized by higher intakes of red and processed meats, sweets and desserts, potatoes, french fries, and refined grains was associated with a higher risk, independent of lifestyle factors.^{115,116}

Two randomized trials tested the whole-diet approach in secondary prevention of CHD (Table). In the Indian Heart Study,¹¹⁷ a semivegetarian diet en-

riched with fruits, vegetables, whole grains, and nuts reduced coronary death by 41% and nonfatal MI by 38%. In the Lyon Diet Heart Study,^{69,70} a Mediterranean diet enriched with ALA reduced CHD death by more than 70%. These findings, together with the results from prospective cohort studies and the Dietary Approaches to Stop Hypertension trials,^{118,119} support the clinical utility of a whole-diet approach in the prevention of cardiovascular disease.

COMBINED EFFECTS OF DIET AND LIFESTYLE

The combination of multiple dietary factors is more powerful than a single factor alone. In the Nurses' Health Study cohort, a diet high in cereal fiber, marine omega-3 fatty acids, and folate and low in trans-fat and GL, with a high ratio of polyunsaturated fat to saturated fat, strongly predicted decreased risk of CHD (relative risk comparing highest with lowest quintiles of the composite score = 0.40; 95% confidence interval, 0.31-0.53).¹²⁰ Also, improvement in these dietary factors explained much of the decline in the incidence of CHD during 14 years of follow-up of the cohort.¹¹¹

Besides diet, several other behavioral factors strongly influence CHD risk. Analyses from the Nurses' Health Study estimated that 82% of CHD events in the study cohort could be potentially prevented by moderate diet and lifestyle modifications.¹²⁰ Among nonsmokers, 74% of coronary events might have been prevented by eating a healthy diet, maintaining a healthy body weight, exercising regularly for half an hour or more daily, and consuming a moderate amount of alcohol (≥ 5 g/d).

Results from several multifactorial primary prevention trials using diet and lifestyle intervention have been largely unimpressive, probably because of poor compliance and inadequate power.¹²² The Oslo Heart Study, however, demonstrated that stopping smoking and increasing the ratio of polyunsaturated to saturated fats in the diet reduced CHD incidence by 47% among men with

higher-than-average serum cholesterol levels.¹²³ In the Lifestyle Heart Study,¹²⁴ a combination of an extremely low-fat diet, exercise, stress management, and yoga significantly reduced progression of atherosclerosis, but the low-fat regimen is unnecessarily rigid and difficult for most people to follow.

AREAS OF UNCERTAINTY

The optimal amounts of monounsaturated and polyunsaturated fats in the diet are still unclear. Intake of linoleic acid is usually recommended not to exceed 10% of energy, in part because of little long-term human experience with such diets, although benefits from higher intake exist for blood lipids. There has been some concern that a high-polyunsaturated-fat diet may increase cancer risk, but this has not been substantiated in large epidemiologic studies.¹²⁵

The optimal balance between omega-3 and omega-6 polyunsaturated fatty acids also remains unsettled. Some have proposed reducing the consumption of linoleic acid to achieve a greater ratio of omega-3 to omega-6 fatty acids in the diet.^{126,127} However, there is little evidence that a higher ratio predicts a lower risk of CHD.¹²⁸ Both omega-3 and omega-6 fatty acids have important roles in reducing CHD risk, probably through different mechanisms. Thus, a good strategy is to substantially increase intake of omega-3 fatty acids from fish and plant sources (because intake for many people is clearly suboptimal) without decreasing intake of linoleic acid. This will improve the ratio and maximize the cardioprotective benefits of both omega-3 and omega-6 fatty acids.

The amount and type of protein in the diet is a matter of debate. Substitution of soy for animal protein reduces LDL-C,¹²⁹ and substituting animal protein for carbohydrates raises HDL-C and lowers triglyceride levels.¹³⁰ Consistent with the metabolic studies, a prospective cohort study found that a moderately high protein intake (24% vs 15% of energy from protein) was associated with a sig-

OPTIMAL DIETS FOR PREVENTION OF CHD

nificantly lower risk of CHD after adjustment for cardiovascular risk factors and dietary fat intake.¹³¹ To avoid an increase in saturated fat intake, the major source of protein in the diet should come from nuts, soybeans, legumes, poultry, and fish.

The role of phytochemicals and antioxidants in the prevention of CHD is promising but unsettled. The cholesterol-lowering effects of plant sterol or stanol (saturated sterols) have been well documented in clinical trials¹³² and commercial products made of these compounds are widely available, but their long-term effects remain to be seen. Six prospective cohort studies have evaluated the association between flavonoid intake and risk of CHD. A significant inverse association was observed in some studies¹³³⁻¹³⁶ but not others.^{137,138} Although a body of experimental evidence has demonstrated the role of antioxidant vitamins in reducing oxidative stress and substantial epidemiologic evidence has linked intake of vitamin E with a lower CHD risk, results from published clinical trials of vitamin E supplements, primarily among patients with clinical CHD, have been largely disappointing.^{139,140} Ongoing primary prevention trials should provide more insights.

Finally, a large and inconclusive literature has examined the relationship between dietary minerals such as calcium, magnesium, zinc, and selenium and risk of CHD.¹⁴¹ Most studies have been based on ecological correlations or case-control analyses. Additional large prospective studies or randomized trials with clinical end points are required to resolve the role of individual minerals from diet or supplements.

CONCLUSIONS

Compelling evidence from metabolic studies, epidemiologic investigations, and clinical trials in the past several decades converges to indicate that at least 3 dietary strategies are effective in preventing CHD: substitute unsaturated fats (especially polyunsaturated fat) for saturated and trans-fats; increase con-

sumption of omega-3 fatty acids from fish oil or plant sources; and consume a diet high in fruits, vegetables, nuts, and whole grains and low in refined grains. A combination of these approaches can confer greater benefits than a single approach. However, simply lowering the percentage of energy from total fat in the diet is unlikely to improve lipid profile or reduce CHD incidence.

Obesity is an important avenue by which diet can influence risk of CHD. However, the relationship between diet, especially dietary fat, and obesity remains controversial. Although reduction in percentage of calories from dietary fat intake is commonly recommended for weight loss, long-term clinical trials have provided no good evidence that reducing dietary fat per se can lead to weight loss.^{141,142} There is a growing consensus that excess calories, whether from carbohydrates or fat, will induce weight gain. A mildly hypocaloric moderate-fat diet, which allows for a great variety in choosing foods, can have better long-term compliance than a typical low-fat diet.¹⁴³ Small short-term studies have suggested roles of several diets in weight control, including a low-GI diet,¹⁴⁴ a high-protein diet,^{145,146} and a diet high in dairy products,¹⁴⁷ but larger and long-term studies are needed.

Although prevailing dietary guidelines emphasize target intake of specific macronutrients (eg, not exceeding 30% of energy from fat),⁷¹ such numerical criteria are not based on solid scientific evidence, and the public finds it difficult to make dietary changes based on such criteria. A variety of options exist for designing attractive and heart-healthy diets, with varying amounts of fat and carbohydrates, as long as the diet embraces healthy types of fat and carbohydrates and provides an appropriate balance in energy intake and expenditure. Evidence is now clear that diets including nonhydrogenated unsaturated fats as the predominant form of dietary fat, whole grains as the main form of carbohydrate, an abundance of fruits and vegetables, and

adequate omega-3 fatty acids can offer significant protection against CHD. Such diets, together with regular physical activity, avoidance of smoking, and maintaining a healthy weight, may prevent the majority of cardiovascular disease in Western populations.

Author Contributions: Study concept and design: Hu, Willett.

Drafting of the manuscript: Hu.

Critical revision of the manuscript for important intellectual content: Hu, Willett.

Obtained funding: Hu.

Funding/Support: This review was supported by research grant HL60712 from the National Institutes of Health. Dr Hu is partly supported by an Established Investigator Award from the American Heart Association.

REFERENCES

- Anitschkow NN. A history of experimentation on arterial atherosclerosis in animals. In: Blumenthal ED, ed. *Cowdry's Arteriosclerosis: A Survey of the Problem*. 2nd ed. Springfield, IL: Charles C Thomas; 1967: 21-44.
- McGill HC. The relationship of dietary cholesterol to serum cholesterol concentration and to atherosclerosis in man. *Am J Clin Nutr*. 1979;32:2664-2702.
- Gordon T. The diet-heart idea: outline of a history. *Am J Epidemiol*. 1988;127:220-225.
- Keys A. *Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease*. Cambridge, Mass: Harvard University Press; 1980.
- Kato H, Tillotson J, Nichaman MZ, Rhoads GG, Hamilton HB. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: serum lipids and diet. *Am J Epidemiol*. 1973;97:372-385.
- Hu FB, Willett WC. Diet, nutrition, and coronary heart disease. In: Douglas PS, ed. *Cardiovascular Health and Disease in Women*. 2nd ed. Philadelphia: WB Saunders; 2002:71-92.
- Keys A, Parlin RW. Serum-cholesterol response to changes in dietary lipids. *Am J Clin Nutr*. 1966;19: 175-181.
- Hegsted DM, McGandy RB, Myers ML, Stare FJ. Quantitative effects of dietary fat on serum cholesterol in man. *Am J Clin Nutr*. 1965;17:281-295.
- Hegsted DM, Ausman LM, Johnson JA, Dallal GE. Dietary fat and serum lipids: an evaluation of the experimental data [published correction appears in Am J Clin Nutr. 1993;58:245]. *Am J Clin Nutr*. 1993;57: 875-883.
- Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins: a meta-analysis of 27 trials. *Arterioscler Thromb*. 1992;12:911-919.
- Yu S, Derr J, Etherton TD, Kris-Etherton P. Plasma cholesterol-predictive equations demonstrate that stearic acid is neutral and monounsaturated fatty acids are hypocholesterolemic. *Am J Clin Nutr*. 1995; 61:1129-1139.
- Hu FB, van Dam RM, Liu S. Diet and risk of type II diabetes: the role of types of fat and carbohydrate. *Diabetologia*. 2001;44:805-817.
- Summers LF, Fielding BA, Bradshaw HA, et al. Substituting dietary saturated fat with polyunsaturated fat changes abdominal fat distribution and improves insulin sensitivity. *Diabetologia*. 2002;45:369-377.
- Meyer KA, Kushi LH, Jacobs DR Jr, Folsom AR. Dietary fat and incidence of type 2 diabetes in older Iowa women. *Diabetes Care*. 2001;24:1528-1535.
- Salmeron J, Hu FB, Manson JE, et al. Dietary fat intake and risk of type 2 diabetes in women. *Am J Clin Nutr*. 2001;73:1019-1026.

OPTIMAL DIETS FOR PREVENTION OF CHD

16. Mensink RP, Katan MB. Effect of dietary *trans* fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. *N Engl J Med*. 1990; 323:439-445.

17. Zock PL, Katan MB. Hydrogenation alternatives: effects of *trans* fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans. *J Lipid Res*. 1992;33:399-410.

18. Nestel P, Noakes M, Bellfog B. Plasma lipoprotein and Lp(a) changes with substitution of elaidic acid for oleic acid in the diet. *J Lipid Res*. 1992;33:1029-1036.

19. Judd JT, Clevidence BA, Muesing RA, Witter J, Sunkin ME, Podczasny JJ. Dietary *trans* fatty acids: effects of plasma lipids and lipoproteins on healthy men and women. *Am J Clin Nutr*. 1994;59:861-868.

20. Judd JT, Baer DJ, Clevidence BA, Kris-Etherton P, Muesing RA, Iwane M. Dietary *cis*- and *trans* monounsaturated and saturated FA and plasma lipids and lipoproteins in men. *Lipids*. 2002;37:123-131.

21. Lichtenstein AH, Ausman LM, Jalbert SM, Schaefer EJ. Effects of different forms of dietary hydrogenated fats on serum lipoprotein cholesterol levels. *N Engl J Med*. 1999;340:1933-1940.

22. Aro A, Jauhainen M, Partanen R, Salminen I, Mularinen M. Stearic acid, trans fatty acids, and dairy fat: effects on serum and lipoprotein lipids, apolipoproteins, lipoprotein(a), and lipid transfer proteins in healthy subjects. *Am J Clin Nutr*. 1997;65:1419-1426.

23. Sundram K, Ismail A, Hays KC, Jayamalar R, Palithamanthan R. Trans (elaidic) fatty acids adversely affect the lipoprotein profile relative to specific saturated fatty acids in humans. *J Nutr*. 1997;127:514S-520S.

24. Lichtenstein AH, Ausman LM, Carrasco W, Jenner JL, Ordovas JM, Schaefer EJ. Hydrogenation impairs the hypolipidemic effect of corn oil in humans: hydrogenation, *trans* fatty acids, and plasma lipids. *Arterioscler Thromb*. 1993;13:154-161.

25. Ascherio A, Katan MB, Zock PL, Stampfer MJ, Willett WC. *Trans* fatty acids and coronary heart disease. *N Engl J Med*. 1999;340:1994-1998.

26. Katan MB, Zock PL. *Trans* fatty acids and their effects on lipoproteins in humans. *Annu Rev Nutr*. 1995;15:473-493.

27. de Roos NM, Bots ML, Siebelink E, Schouten E, Katan MB. Flow-mediated vasodilation is not impaired when HDL-cholesterol is lowered by substituting carbohydrates for monounsaturated fat. *Br J Nutr*. 2001;86:181-188.

28. Hill EG, Johnson SB, Lawson LD, Mahfouz MM, Holman RT. Perturbation of the metabolism of essential fatty acids by dietary hydrogenated vegetable oil. *Proc Natl Acad Sci U S A*. 1982;79:953-957.

29. Kinsella JE, Bruckner G, Mai J, Shimp J. Metabolism of *trans* fatty acids with emphasis on the effects of *trans*, *trans*-octadecadienoate on lipid composition, essential fatty acid, and prostaglandins: an overview. *Am J Clin Nutr*. 1981;34:2307-2318.

30. Lovejoy JC. Dietary fatty acids and insulin resistance. *Curr Atheroscler Rep*. 1999;1:215-220.

31. Kromhout D, Menotti A, Bloomberg B, et al. Dietary saturated and *trans* fatty acids and cholesterol and 25-year mortality from coronary heart disease: the Seven Countries Study. *Prev Med*. 1995;24:308-315.

32. Garcia-Palmieri MR, Sorlie P, Tillotson J, Costas R Jr, Cordero E, Rodriguez M. Relationship of dietary intake to subsequent coronary heart disease incidence: the Puerto Rico Heart Health Program. *Am J Clin Nutr*. 1980;33:1818-1827.

33. Gordon T, Kagan A, Garcia-Palmieri M, et al. Diet and its relation to coronary heart disease and death in three populations. *Circulation*. 1981;63:500-515.

34. Shekelle RB, Shryock AM, Paul O, et al. Diet, serum cholesterol, and death from coronary heart disease: the Western Electric Study. *N Engl J Med*. 1981;304:65-70.

35. McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. Ten-year incidence of coronary heart disease in the Honolulu Heart Program: relationship to nutrient intake. *Am J Epidemiol*. 1984;119:667-676.

36. Kushi LH, Lew RA, Stare FJ, et al. Diet and 20-year mortality from coronary heart disease: the Ireland-Boston Diet-Heart Study. *N Engl J Med*. 1985;312:811-818.

37. Kromhout D, de Lezenne Coulander C. Diet, prevalence and 10-year mortality from coronary heart disease in 871 middle-aged men: the Zutphen Study. *Am J Epidemiol*. 1984;119:733-741.

38. Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer MJ, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow-up study in the United States. *BMJ*. 1996;313:84-90.

39. Pöltinen P, Ascherio A, Korhonen P, et al. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men: the ATBC Study. *Am J Epidemiol*. 1997;145:876-887.

40. Hu FB, Stampfer MJ, Manson JE, et al. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med*. 1997;337:1491-1499.

41. Willett WC. *Nutritional Epidemiology*. 2nd ed. New York, NY: Oxford University Press; 1998.

42. Hu FB, Stampfer MJ, Rimm EB, et al. A prospective study of egg consumption and risk of cardiovascular disease in men and women. *JAMA*. 1999;281:1387-1394.

43. Oomen C, Ocke MC, Feskens JM, van Erp-Baur MJ, Kok FJ, Kromhout D. Association between *trans* fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. *Lancet*. 2001;357:746-751.

44. Lemaitre RN, King IB, Raghunathan TE, et al. Cell membrane *trans*-fatty acids and the risk of primary cardiac arrest. *Circulation*. 2002;105:697-701.

45. Roberts TL, Wood DA, Riendersma RA, Gallagher PJ, Lampe FC. *Trans* isomers of oleic and linoleic acids in adipose tissue and sudden cardiac death. *Lancet*. 1995;345:278-282.

46. Dayton S, Pearce ML, Hashimoto S, Dixon WJ, Tomiyasu U. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. *Circulation*. 1969;40(suppl 2):1-63.

47. Turpeinen O, Karvonen MJ, Pekkarinen M, Miettinen M, Eloso R, Paavilainen E. Dietary prevention of coronary heart disease: the Finnish Mental Hospital Study. *Int J Epidemiol*. 1979;8:99-118.

48. Leren P. The Oslo Diet-Heart Study. *Acta Med Scand*. 1966;466(suppl):5-92.

49. Leren P. The Oslo Diet-Heart Study: eleven-year report. *Circulation*. 1970;42:935-942.

50. Morris JN, Ball KP, Antonis A, et al. Controlled trial of soya-bean oil in myocardial infarction. *Lancet*. 1968;2:693-699.

51. Frantz ID Jr, Dawson EA, Ashman PL, et al. Test of effect of lipid lowering by diet on cardiovascular risk: the Minnesota Coronary Survey. *Arteriosclerosis*. 1989;9:129-135.

52. Ball KP, Hanington E, McAllen PM, et al. Low-fat diet in myocardial infarction: a controlled trial. *Lancet*. 1965;2:501-504.

53. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). *Lancet*. 1989;2:757-761.

54. Kang JX, Leaf A. Antiarrhythmic effects of polyunsaturated fatty acids: recent studies. *Circulation*. 1996;94:1771-1780.

55. Connor SL, Connor WE. Are fish oils beneficial in the prevention and treatment of coronary artery disease? *Am J Clin Nutr*. 1997;66(4 suppl):1020S-1031S.

56. Kromhout D, Bosscher EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med*. 1985;312:1205-1209.

57. Marckmann P, Gronbaek M. Fish consumption and coronary heart disease mortality: a systematic review of prospective cohort studies. *Eur J Clin Nutr*. 1999;53:585-590.

58. Oomen CM, Feskens EJ, Rasanen L, et al. Fish consumption and coronary heart disease mortality in Finland, Italy, and the Netherlands. *Am J Epidemiol*. 2000;151:999-1006.

59. Rissanen T, Voutilainen S, Nyysönen K, Lakka TA, Salonen JT. Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Circulation*. 2000;102:2677-2679.

60. Hu FB, Bronner L, Willett WC, et al. Fish and omega-3 fatty acid and risk of coronary heart disease in women. *JAMA*. 2002;287:1815-1821.

61. Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med*. 2002;346:1113-1118.

62. Tavani A, Pelucchi C, Negri E, Bertuzzi M, La Vecchia C. n-3 Polyunsaturated fatty acids, fish, and non-fatal acute myocardial infarction. *Circulation*. 2001;104:2269-2272.

63. Hu FB, Stampfer MJ, Manson JE, et al. Dietary intake of alpha-linolenic acid and risk of ischemic heart disease among women. *Am J Clin Nutr*. 1999;69:890-897.

64. Doepleit TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial. *Proc Soc Exp Biol Med*. 1992;200:177-182.

65. Oomen CM, Ocke MC, Feskens JM, Kok FJ, Kromhout D. *n*-3 Linolenic acid intake is not beneficially associated with 10-y risk of coronary artery disease incidence: the Zutphen Elderly Study. *Am J Clin Nutr*. 2001;74:457-463.

66. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results from the GISSI-Prevenzione trial. *Lancet*. 1999;354:447-455.

67. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation*. 2002;105:1897-1903.

68. Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moskin M. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian Experiment of Infarct Survival 4. *Cardiovasc Drugs Ther*. 1997;11:485-491.

69. de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet*. 1994;343:1454-1459.

70. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99:779-785.

71. US Department of Agriculture/US Department of Health and Human Services. *Nutrition and Your Health: Dietary Guidelines for Americans*. Washington, DC: US Government Printing Office; 2000. Homes and Gardens Bulletin 232.

72. Krauss RM, Eckel RH, Howard B, et al. AHA dietary guidelines revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation*. 2000;102:2284-2299.

73. Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr*. 1981;34:362-366.

OPTIMAL DIETS FOR PREVENTION OF CHD

74. Wolever TM, Jenkins DJ, Jenkins AL, Josse RG. The glycemic Index: methodology and clinical implications. *Am J Clin Nutr.* 1991;54:846-854.

75. Jenkins DJ, Kendall CW, Augustin LS, et al. Glycemic index: overview of implications in health and disease. *Am J Clin Nutr.* 2002;76:266S-273S.

76. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA.* 1997;277:472-477.

77. Salmeron J, Ascherio A, Rimm EB, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care.* 1997;20:545-550.

78. Liu S, Manson JE, Stampfer MJ, et al. Dietary glycemic load assessed by food frequency questionnaire in relation to plasma high-density lipoprotein cholesterol and fasting triglycerides in postmenopausal women. *Am J Clin Nutr.* 2001;73:560-566.

79. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load and risk of myocardial infarction in women. *Am J Clin Nutr.* 2000; 71:1455-1461.

80. Jeppesen J, Schaaf P, Jones C, Zhou MY, Chen YD, Reaven GM. Effects of low-fat, high-carbohydrate diets on risk factors for ischemic heart disease in postmenopausal women [published correction appears in *Am J Clin Nutr.* 1997;66:437]. *Am J Clin Nutr.* 1997;65:1027-1033.

81. Liu S, Burling JE, Sesso HD, Rimm EB, Willett WC, Manson JE. A prospective study of dietary fiber intake and risk of cardiovascular disease among women. *J Am Coll Cardiol.* 2002;39:49-56.

82. Rimm EB, Ascherio A, Giovannucci E, Spiegelman D, Stampfer MJ, Willett WC. Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *JAMA.* 1996;275:417-451.

83. Pietinen P, Rimm EB, Karhonen P, et al. Intake of dietary fiber and risk of coronary heart disease in a cohort of Finnish men: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Circulation.* 1996; 94:2720-2727.

84. Wolk AM, Manson JE, Stampfer MJ, et al. Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. *JAMA.* 1999;281: 1998-2004.

85. Jacobs DR, Pereira MA, Meyer KA, Kushi LH. Fiber from whole grains, but not refined grains, is inversely associated with all-cause mortality in older women: the Iowa Women's Health Study. *J Am Coll Nutr.* 2000;19(3 suppl):326S-330S.

86. Rimm E, Willett WC, Hu FB, et al. Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. *JAMA.* 1998; 279:359-365.

87. Voutilainen S, Rissanen TH, Virtanen J, Lakka TA, Salonen JT. Low dietary folate intake is associated with an excess incidence of acute coronary events: the Kuopio Ischemic Heart Disease Risk Factor Study. *Circulation.* 2001;103:2674-2680.

88. Bazzano LA, He J, Ogden LG, et al. Dietary intake of folate and risk of stroke in US men and women: NHANES-I Epidemiologic Follow-up Study. *Stroke.* 2002;33:1183-1189.

89. Loria CM, Ingram DD, Feldman JJ, Wright JD, Madans JH. Serum folate and cardiovascular disease mortality among US men and women. *Arch Intern Med.* 2000;160:3258-3262.

90. Voutilainen S, Lakka TA, Poriokala-Saralaho E, Rissanen T, Kaplan GA, Salonen JT. Low serum folate concentrations are associated with an excess incidence of acute coronary events: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Eur J Clin Nutr.* 2000;54:424-428.

91. Vermeulen EG, Stenhouwer CD, Twisk JW, et al. Effect of homocysteine-lowering treatment with folic acid plus vitamin B6 on progression of subclinical atherosclerosis: a randomized, placebo-controlled trial. *Lancet.* 2000;355:517-522.

92. Schnyder G, Roffi M, Pin R, et al. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. *N Engl J Med.* 2001;345:1593-1600.

93. Schnyder G, Roffi M, Flammer Y, Pin R, Hess OM. Effect of homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 on clinical outcome after percutaneous coronary intervention: the Swiss Heart Study: a randomized controlled trial. *JAMA.* 2002; 288:973-979.

94. Boston AG, Selhub J, Jacques PF, Rosenberg IH. Power shortage: clinical trials testing the "homocysteine hypothesis" against a background of folic acid-fortified cereal grain flour. *Ann Intern Med.* 2001; 135:133-137.

95. Hu FB, Stampfer MJ, Manson JE, et al. Dietary saturated fat and their food sources in relation to the risk of coronary heart disease in women. *Am J Clin Nutr.* 1999;70:1001-1008.

96. Fraser GE, Sabate J, Beeson WL, Strahan TM. A possible protective effect of nut consumption on risk of coronary heart disease: the Adventist Health Study. *Arch Intern Med.* 1992;152:1416-1424.

97. Fraser GE, Shavlik DJ. Risk factors for all-cause and coronary heart disease mortality in the oldest-old: the Adventist Health Study. *Arch Intern Med.* 1997;157: 2249-2258.

98. Hu FB, Stampfer MJ, Manson JE, et al. Frequent nut consumption and risk of coronary heart disease: prospective cohort study. *BMJ.* 1998;317:1341-1345.

99. Brown L, Sacks F, Rosner B, Willett WC. Nut consumption and risk of coronary heart disease in patients with myocardial infarction [abstract]. *FASEB J.* 1999;13:A4332.

100. Ellsworth JL, Kushi LH, Folsom AR. Frequent nut intake and risk of death from coronary heart disease and all causes in postmenopausal women: the Iowa Women's Health Study. *Nutr Metab Cardiovasc Dis.* 2001;11:372-377.

101. Albert CM, Gaziano JM, Willett WC, Manson JE. Nut consumption and decreased risk of sudden cardiac death in the physicians' health study. *Arch Intern Med.* 2002;162:1382-1387.

102. Kris-Etherton PM, Zhao G, Binko AE, Coval SM, Etherton TD. The effects of nuts on coronary heart disease risk. *Nutr Rev.* 2001;59:103-111.

103. Knekt P, Reunanan A, Jarvinen R, Seppanen R, Heliovaara M, Aromaa A. Antioxidant vitamin intake and coronary mortality in a longitudinal population study. *Am J Epidemiol.* 1994;139:1180-1189.

104. Gillman MW, Cupples LA, Gagnon D, et al. Protective effect of fruits and vegetables on development of stroke in men. *JAMA.* 1995;273:1113-1117.

105. Gaziano JM, Manson JE, Branch LG, Colditz GA, Willett WC, Buring JE. A prospective study of consumption of carotenoids in fruits and vegetables and decreased cardiovascular mortality in the elderly. *Ann Epidemiol.* 1995;5:255-260.

106. Joshipura KJ, Ascherio A, Manson JE, et al. Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA.* 1999;282:1233-1239.

107. Joshipura KJ, Hu FB, Manson JE, et al. The effect of fruit and vegetable intake on risk for coronary heart disease. *Ann Intern Med.* 2001;134:1106-1114.

108. Liu S, Manson JE, Lee IM, et al. Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health Study. *Am J Clin Nutr.* 2000;72: 922-928.

109. Liu S, Lee IM, Ajani U, Cole SR, Buring JE, Manson JE. Intake of vegetables rich in carotenoids and risk of coronary heart disease in men: the Physicians' Health Study. *Int J Epidemiol.* 2001;30:130-135.

110. Bazzano LA, He J, Ogden LG, et al. Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Am J Clin Nutr.* 2002;76:93-99.

111. Jacobs DR, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa Women's Health Study. *Am J Clin Nutr.* 1998; 68:248-257.

112. Liu S, Stampfer MJ, Hu FB, et al. Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. *Am J Clin Nutr.* 1999;70:412-419.

113. Liu S, Manson JE, Stampfer MJ, et al. Whole grain consumption and risk of ischemic stroke in women: a prospective study. *JAMA.* 2000;284:1534-1540.

114. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol.* 2002;13:3-9.

115. Hu FB, Rimm EB, Stampfer MJ, Ascherio A, Spiegelman D, Willett WC. Prospective study of major dietary patterns and risk of coronary heart disease in men. *Am J Clin Nutr.* 2000;72:912-921.

116. Fung TT, Willett WC, Stampfer MJ, Manson JE, Hu FB. Dietary patterns and risk of coronary heart disease in women. *Arch Intern Med.* 2001;161:1857-1862.

117. Singh RB, Rastogi SS, Verman R, et al. Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one year follow up. *BMJ.* 1992;304:1015-1019.

118. Appel L, Moore TJ, Obarzanek E, for the DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med.* 1997;336:1117-1124.

119. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med.* 2001;344:3-10.

120. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med.* 2000;343:16-22.

121. Hu FB, Stampfer MJ, Manson JE, et al. Trends in the incidence of coronary heart disease and changes in diet and lifestyle in women. *N Engl J Med.* 2000; 343:530-537.

122. Miettinen TA, Strandberg TE. Implications of recent results on long term multifactorial primary prevention of cardiovascular diseases. *Ann Med.* 1992; 24:85-89.

123. Hjermann I, Velle Byre K, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease: report from the Oslo Study Group of a randomised trial in healthy men. *Lancet.* 1981;2:1303-1310.

124. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease [published correction appears in *JAMA.* 1999; 281:1380]. *JAMA.* 1998;280:2001-2007.

125. Zock PL, Katan MB. Linoleic acid intake and cancer risk: a review and meta-analysis. *Am J Clin Nutr.* 1998;68:142-153.

126. Leaf A. On the reanalysis of the GISSI-Prevenzione. *Circulation.* 2002;105:1874-1875.

127. Berry EM. Dietary fatty acids in the management of diabetes mellitus. *Am J Clin Nutr.* 1997;66(4 suppl):991S-997S.

128. Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review. *J Am Coll Nutr.* 2001;20:5-19.

129. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med.* 1995;333:276-282.

130. Wolfe BM. Potential role of raising dietary protein intake for reducing risk of atherosclerosis. *Can J Cardiol.* 1995;11(suppl G):127G-131G.

OPTIMAL DIETS FOR PREVENTION OF CHD

131. Hu FB, Stampfer MJ, Manson JE, et al. Dietary protein and risk of coronary heart disease in women. *Am J Clin Nutr.* 1999;70:221-227.

132. Law M. Plant sterol and stanol margarines and health. *BMJ.* 2000;320:861-864.

133. Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet.* 1993;342:1007-1011.

134. Knekt P, Jarvinen R, Reunanen A, Maatela J. Flavonoid intake and coronary mortality in Finland: a cohort study. *BMJ.* 1996;312:478-481.

135. Yochum L, Kushi LH, Meyer K, Folsom AR. Dietary flavonoid intake and risk of cardiovascular disease in postmenopausal women [published correction appears in *Am J Epidemiol.* 1999;150:432]. *Am J Epidemiol.* 1999;149:943-949.

136. Gudejnsse JM, Launer LJ, Van der Kulp DA, Hofman A, Witteman JC. Inverse association of tea and flavonoid intakes with incident myocardial infarction: the Rotterdam Study. *Am J Clin Nutr.* 2002;75: 880-886.

137. Rimm EB, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Relation between intake of flavonoids and risk for coronary heart disease in male health professionals. *Ann Intern Med.* 1996;125:384-389.

138. Hertog MG, Sweetnam PM, Fehily AM, Elwood PC, Kromhout D. Antioxidant flavonoids and ischemic heart disease in a Welsh population of men: the Caerphilly Study. *Am J Clin Nutr.* 1997;65:1489-1494.

139. Pruthi S, Allison TG, Hensrud DD. Vitamin E supplementation in the prevention of coronary heart disease. *Mayo Clin Proc.* 2001;76:1131-1136.

140. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20536 high-risk individuals: a randomized placebo-controlled trial. *Lancet.* 2002; 360:23-33.

141. Pirozzi S, Summerbell C, Cameron C, Glasziou P. Advice on low-fat diets for obesity (Cochrane Review on CD-ROM). Oxford, England: Cochrane Library, Update Software; 2002; issue 2.

142. Willett WC. Dietary fat plays a major role in obesity: no. *Obes Rev.* 2002;3:59-68.

143. McManus K, Antinoro L, Sacks F. A randomized controlled trial of a moderate-fat, low-energy diet compared with a low fat, low-energy diet for weight loss in overweight adults. *Int J Obes Relat Metab Disord.* 2001;25:1503-1511.

144. Ludwig DS. The glycemic Index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA.* 2002;287:2414-2423.

145. Skov AR, Toubro S, Ronn B, Holm L, Astrup A. Randomized trial on protein vs carbohydrate in ad libitum fat reduced diet for the treatment of obesity. *Int J Obes Relat Metab Disord.* 1999;23: 528-536.

146. Baba NH, Sawaya S, Torbay N, Habbal Z, Azar S, Hashim SA. High protein vs high carbohydrate hypoenergetic diet for the treatment of obese hyperinsulinemic subjects. *Int J Obes Relat Metab Disord.* 1999;23:1202-1206.

147. Zemel MB. Regulation of adiposity and obesity risk by dietary calcium: mechanisms and implications. *J Am Coll Nutr.* 2002;21:146S-151S.

To spend too much time in studies is sloth; to use them too much for ornament, is affectation; to make judgment wholly by their rules, is the humour of a scholar. . . . Read not to contradict and confute; nor to believe and take for granted; nor to find talk and discourse; but to weigh and consider. Some books are to be tasted, others to be swallowed, and some few to be chewed and digested. . . . Reading maketh a full man; conference a ready man; and writing an exact man. . . . Histories make men wise; poets witty; the mathematics subtile; natural philosophy deep; moral grave; logic and rhetoric able to contend.

—Francis Bacon (1561-1626)